REVIEW PAPER

Clinical trials on silver nanoparticles for wound healing (review)

Zakieh Boroumand [1], Nahid Golmakani [2*], Safieh Boroumand [3]

[1]*School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran*
[2]*Department of Midwifery, Evidence-based Health Care Research Center, School of Nursing and Midwifery, Mashhad University of Medical Sciences, Mashhad, Iran*
[3]*Department of Medical Nanotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran*

ABSTRACT

Despite the prevalence of different kinds of wounds among people around the world, challenges ahead for managing wound healing continues. One of the most important issues for wound healing is infection that can delay healing process. Also, drug-resistant infections are growing as a worrying challenge in medicine. A lot of studies done over different methods to improve wound healing process, which in this regard, anti-bacterial nanoparticles have emerged to market for wound healing. Silver nanoparticles are the first kinds of nanoparticles that emerged in market as a wound dressing for wound healing and some of studies declared their clinical results for silver nanoparticles wound dressing for different kinds of wounds. In this review, we tried to browse clinical trials through using silver nanoparticles for wound healing to peruse the efficacy of silver nanoparticles dressing. The need for more study about efficacy and safety of silver nanoparticles is still a question.

Keywords: *Drug-resistant infection, Silver nanoparticles, Wound*

How to cite this article

Boroumand Z, Golmakani N, Boroumand S. Clinical Trials on Silver nanoparticles for wound healing (review). Nanomed J. 2018; 5(4): 186-191. DOI: 10.22038/nmj.2018.05.00001

INTRODUCTION

During lifetime different events can lead to wound, around one billion people suffer acute or/and chronic wounds. Wound healing is a complex biological process consisting four different phases (hemostasis, inflammation, proliferation, maturation) [1]. The importance of improving healing process of wound is clear and many studies have been done to improve wound healing process. Despite the prevalence of wounds, managing skin damages by medical technology is still inefficient. Many disturbing factor in healing processes can lead to inappropriate healing in dermal and epidermal layers. Confining infection as a disturbing factor is one of challenges for wound healing process [2]. As a challenging and rapidly growing research field, nanotechnology have emerged in wound healing. Many researchers have been tested different nanomaterials for wound healing and some of them like Ag, ZnO, Au, Cu and FeO nanoparticles showed acceptable results on healing process [1].

Silver have been used as an antiseptic agent which can be a broad spectrum antibiotic. It has emerged into ointments and creams since 1968 for topical usages to prevent infection [3, 4]. Blocking the cellular respiration, silver act as an antibacterial agent. Also free silver disrupt bacterial cell membrane function [5]. The important note for Silver nanoparticles is that these kinds of nanoparticles are able to overcome some of the antibiotic-resistant bacteria which can reduce the mortality and the prolonged treatment cost [6]. On the other side, by anti-inflammatory effects and neovascularization, silver nanoparticles can also accelerate the wound healing process [7, 8].

By in vitro and in vivo studies, many researchers has been tested Silver nanoparticle for its antibacterial properties [5]. Silver nanoparticles (AgNPs) is the most commonly used nanoparticles for wound healing, which has emerged in commercially available wound dressing like Acticoat, PolyMem Silver and etc. [2, 9-11]. These kinds of dressing can confine the unwanted release of nanoparticles into the wound area, so

* *Corresponding Author Email: golmakanin@mums.ac.ir*
Note. This manuscript was submitted on August 1, 2018; approved on September 1, 2018

less probable toxicity might be happen.

Silver nanoparticles have examined for different kinds of ulcers and wounds by researchers, but coming into clinic make it important to investigate its effects on wound in human. Here we mention some clinical trials on wound healing by silver nanoparticles. However, most of the clinical trials over wound healing properties of AgNPs have been used on the burns.

MATERIALS AND METHODS

We tried to review all randomized controlled clinical trials which have been done over silver nanoparticles containing dressing for wound healing. Different sources such as Information Sciences Institute (ISI), PubMed, Google Scholar, Scopus, and Science Direct were used to collect data.

Facing with a big challenge

One of the challenges for pharmaceutical industry is finding an appropriate prevention and treatment for infections causing by bacteria, viruses, fungi, and parasites.

This issue becomes more important in the case of antimicrobial resistance (AMR). AMR related rising mortality because of misusing the existing antibiotics and lack of novel antibiotic agents. Bacterial resistance to conventional antibiotics which is a significant threat to public health make it necessary to find alternative strategies for overcoming this challenge [12]. Using nanoscale materials, as an alternative, is a new promising approach to defeat bacterial resistance. Nanoscale material can interact to the bacteria and act as antibacterial agent via different mechanisms which can be as a solution for bacterial resistance [13, 14].

The antibacterial mechanisms of nanoparticles are different for each kinds of nanoparticles. Nitric oxide-releasing nanoparticles (NO NPs), chitosan-containing nanoparticles (chitosan NPs), silver-containing nanoparticles (Ag NPs), copper-containing nanoparticles, titanium dioxide-containing nanoparticles (TiO2 NPs), zinc oxide-containing nanoparticles (ZnO NPs), and magnesium-containing nanoparticles act as antibacterial agent in different ways. Silver nanoparticles have received considerable attention as antibacterial agent among other metallic nanoparticles and act as antibacterial agent by different mechanisms [13].

Synthesis of silver nanoparticles

Silver nanoparticles find a wide popularity among other nanoparticles for its significant antibacterial properties, however its unique optical, electronic, and antibacterial properties are valuable too. Nanoparticles have been synthesized by two important approaches, top-down and bottom-up, which top-down methods used bulk material to reach to nano scaled material and bottom-up pack several atoms, or molecules with molecules, or clusters with clusters [15-17]. Different methods have been reported to synthesis silver nanoparticles, these methods can be divided to chemical, physical, photochemical and biological methods. It is not unexpected that each of these methods has its own advantages and disadvantages, however as an easy method to synthesis silver nanoparticles, chemical methods have been used more than other methods. Reduction of silver ions frequently used to synthesis silver nanoparticles in different studies, the shape and dispersion of nanoparticles can be control by different reducing agents. Metal precursors, reducing agent and stabilizing/capping agents are three main component for chemical synthesis of silver nanoparticles [18].

In the case of physical method, a tube furnace at atmospheric pressure can be used to synthesis silver nanoparticles by evaporation-condensation [19]. Spark discharging and pyrolysis are conventional physical methods for synthesis of AgNPs [20, 21].

Due to concerns about toxicity of chemical agents that use for chemical synthesis of silver nanoparticles, research for safe and reliable approach continues. In this regard, instead of chemical reducing agents, biologically derived reducing agents are used. Other items such as microbes (bacteria and fungi),also are used for synthesis of silver nanoparticles [22, 23].

Antibacterial mechanism of silver nanoparticles

Ag NPs use numerous antibacterial mechanism which reduce the possibility of resistance developing to Ag NPs. Ag dissolves in aqueous solution and Ag^+ ions form which act as antimicrobial agent (Fig 1). One of the antibacterial mechanisms of Ag + ions is due to their interaction with sulfur and phosphorus groups in the structure of proteins of the cell wall and plasma membrane of bacteria that lead to dysfunction of this protein that threats organisms life [6]. On the other hand,

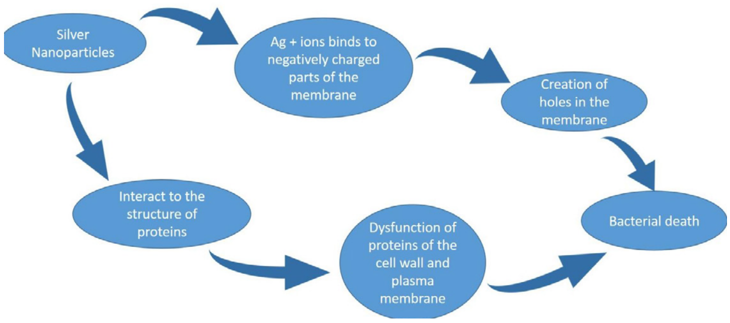

Fig 1. Antibacterial mechanisms of silver nanoparticles

Ag + ions binds to negatively charged parts of the membrane which creates holes in the membrane, cause cytoplasmic contents flow out of the cell, therefore the H+ gradient dissipate across the membrane and finally cause cell death [24]. In the following, existence of Ag + ions inside the cell can disturb the function of electron transport chain of the bacteria. Ag + ions also binds to DNA and RNA of the bacteria and inhibit cell division [13].

Wound dressing

Among all applications of silver nanoparticles, its antibacterial properties were taken into consideration especially for biomedical applications. Infections, as a big challenge, used up a lot of time and cost for years, also emerging antibiotic resistance as a critical problem make it indispensable to find an alternative for managing infection.

Silver has been used as an antibacterial agent for years which nowadays, taking the advantages of nano size materials, silver nanoparticles is emerging into wound dressing criteria. A lot of studies evaluated the efficacy of silver nanoparticles as an antibacterial agent which include in vitro and in vivo studies and now silver nanoparticles are getting to clinical usage as commercially available products. However clinical trials are continuing for finding any new evidence for benefits or side effects of silver nanoparticles. The most studies over silver nanoparticles have been carried on burns, however other kinds of wounds like diabetic ulcers also have been studied.

One of the commercially available AgNPs containing wound dressing is Acticoat (average size of nanoparticles is 15 nm) which some of case reports for Acticoat over wound healing are available in Smith and Nephew Company's site, also many studies have been done to find its efficacy and probable adverse effects. Tredge (1998), compared Acticoat vs silver nitrate solution for burn wounds in 30 patient. Their result showed that the incidence of sepsis was less in Acticoat group, also this group had less pain in comparison to silver nitrate solution [25].

The efficacy of Acticoat for primary burn injuries and other skin injuries in premature neonates evaluated by Rustogi. In this study, re-epithelialization happened in all wounds, also positive blood culture and wound infection were not appeared during treatment [26]. In another study, Fong (2005), determinate the effectiveness of Acticoat to treat early burn wounds in comparison with Silvazine (silver sulphadiazine and chlorhexidine digluconate cream). Acticoat reduced the incidence of burn wound cellulitis, also comparing Silvazine, reduced the overall cost of antibiotic usage [27]. The effectiveness of silver nanoparticles for healing second degree burn wound was evaluated in 199 patients in three groups, silver nanoparticle dressing (group A), 1% silver sulfadiazine cream (group B) and Vaseline gauze (group C). In comparison with group C, reduction in bacterium colonization on wounds was similar for groups A and B, but overall wound healing time was shorter in group A [28].

In another comparative study, the Acticoat vs Silvazine effectiveness compared for burns dressing in pediatrics, and result was that the need for grafting was more in Silvazine group vs Acticoat group, and the time taken for re-epithelialization after grafting was less in Acticoat group. Although, Acticoat reduced long term scar management versus Silvazine [29]. Continuing research over this issue, Acticoat used for exfoliative wounds, which in this study Acticoat showed acceptable bacterial protection in the wound area and promote wound healing process [30].

Also nanocrystalline silver used for Lymphatic ulcers by Forner-Cordero, in this study 8 patients with lymphatic ulcer were treated with commercially available wound dressings, Acticoat, Algisit and Allevyn. Their protocol to heal lymphatic ulcer were effective to cure ulcers during 1 to 9 weeks and was accepted by patients [31]. Continuing studies, Nanosilver crystalline wound dressing evaluated to cure venous leg ulcers with increased bacterial burden and chronic inflammation. In result, the reduction in wound bacteria and inflammation promoted healing process of venous leg ulcers [32]. Acticoat used for post-cardiac surgery mediastinitis in 4 patients, In spite of applying vacuum-assisted closure (VAC) therapy, physicians were faced to persistently positive microbiological cultures at all 4 patients. In this study, Acticoat medication resulted to negative cultures for all 4 patient within a maximum of 72 h [33].

The efficacy of nanocrystalline silver and cadexomer iodine compared for preventing infection in leg ulcers, immediate reduction in wound size was obtained by the nanocrystalline silver in comparison to cadexomer iodine [34]. Nanocrystalline silver wound dressing and hydro surgical debridement compared for Gustilo/ Anderson type II and III fractures. Positive culture and clinical infection were confirmed prior using nanocrystalline silver wound dressing and hydro-surgical debridement. In this study, nanocrystalin silver was able to confine infection and improved wound healing [35].

Another study, Acticoat vs plain gauze for initial post debridement management of military wounds, wound healing process were examined in 76 patients via microbiological assessment. This study did not reveal differences in wound healing and colonization between 2 groups, while unpleasant odor reduced for Acticoat group [36].

Nanocrystalline silver dressing (Acticoat^{R}) compared to regular silver sulfadiazine dressing (control) by Masjedi, Qualitative wound score was more in Acticoat^{R} group, also the healing time was shorter in comparison to control group [37]. Topical silver nano gel vs conventional dressing was tested by Sharma, the results showed good antibacterial and anti-inflammatory effects in wound area [38].

When nanosilver dressing vs Povidone iodine dressing tested for chronic diabetic foot ulcers, it was shown that Nanosilver promote healing process and hospital stay was shorter in nanosilver group [39]. Silver nanoparticels for anorectal surgery evaluated by Wang that in their result the rate of epithelialization was significantly rapid vs control group, wound healing process improved by using silver nanoparticles [40].

As it is not unexpected each dressing might have its imperfection, comparing Acticoat dressing to Aquacel Ag dressing indicated same healing development and bacterial control, but Aquacel Ag dressing was more cost, effective and comfort for the patient [41].

Toxicity is probably another item which can be concern for using Acticoat dressing or silver nanoparticles containing dressing that is mentioned in some studies. Trop et al. declared that using Acticoat dressing for burn patients lead to raised liver enzymes along emersion of argyria like symptoms [42].

Another important concern about silver nanoparticles is for its probable unwanted or toxic effects to environment, threat of silver nanoparticles to soil, water and alive creatures. Also bacterial resistance to silver nanoparticles among losing the beneficial microbes might be a crucial concern [43].

DISCUSSION

The process of wound healing can be affected by different factors which can promote or postpone the healing process. One of the most important factors is infection in wound area that can prolong healing time which also can increase morbidity or mortality via resistance to antibiotic. Prevention of infection in wound area can be crucial for wound healing, different kinds of strategies have been used for preventing wound area infections [1, 5]. Because of antibiotic resistance, other kinds of antibacterial agent emerge such as antibacterial nanoparticles.

Silver nanoparticles evaluated in different studies for its antibacterial properties that can affect the healing process. It proved by different studies that silver nanoparticles can eliminate infection so can promote wound healing process. In addition, different studies proved that silver nanoparticles can improve re-epithelialization in wound area. Most of studies over wound healing properties reveal the efficacy of silver nanoparticle containing dressing to improve healing of different kinds of wounds, but it is felt a significant shortage over clinical trials for evaluating the probable toxicity and side effects of silver nanoparticles dressing.

CONCLUSION

Most studies declared that silver nanoparticles dressing has the potential to be used as an effective antibacterial agent for wound healing. However, clinical trial over the possible toxicity via dermal exposure are not sufficient enough, so more clinical study recommend for additional study over the probable toxicity via dermal exposure of silver nanoparticles.

ACKNOWLEDGEMENTS

Support from Mashhad University of Medical Sciences is acknowledged.

REFERENCES

1. Rex Jeya Rajkumar S, MSA Muthukumar Nadar, Paulraj Mosae Selvakumar. Nanotechnology in Wound Healing-A Review. Glob J Nano. 2017; 3(1): 1-4.
2. Nam G, Rangasamy S, Purushothaman B, Song JM. The application of bactericidal silver nanoparticles in wound treatment. Nanomater Nanotechnol. 2015; 5-23.
3. Fox CL. Silver sulfadiazine—a new topical therapy for pseudomonas in burns: therapy of pseudomonas infection in burns. Arch Surg. 1968; 96(2): 184-188.
4. Hoffmann S. Silver sulfadiazine: an antibacterial agent for topical use in burns. Scand J Plast Reconstr Surg. 1984; 18(1): 119-126.
5. Fong J, Wood F. Nanocrystalline silver dressings in wound management: a review. Int J Nanomedicine. 2006; 1(4): 441-449.
6. Lara HH, Ayala-Núnez NV, Turrent LdCI, Padilla CR. Bactericidal effect of silver nanoparticles against multidrug-resistant bacteria. World J Microbiol Biotechnol. 2010; 26(4): 615-621.
7. Nadworny PL, Wang J, Tredget EE, Burrell RE. Anti-inflammatory activity of nanocrystalline silver in a porcine contact dermatitis model. Nanomedicine. 2008; 4(3): 241-251.
8. Lansdown AB. A pharmacological and toxicological profile of silver as an antimicrobial agent in medical devices. Adv Pharmacol Sci. 2010; 2010: 910686.
9. Pannerselvam B, Jothinathan MKD, Rajenderan M, Perumal P, Thangavelu KP, Kim HJ, Rangarajulu, SK. An in vitro study on the burn wound healing activity of cotton fabrics incorporated with phytosynthesized silver nanoparticles in male Wistar albino rats. Eur J Pharm Sci. 2017; 100: 187-196.
10. Boonkaew B, Kempf M, Kimble R, Supaphol P, Cuttle L. Antimicrobial efficacy of a novel silver hydrogel dressing compared to two common silver burn wound dressings: Acticoat™ and PolyMem Silver®. Burns. 2014; 40(1): 89-96.
11. Dunn K, Edwards-Jones V. The role of Acticoat™ with nanocrystalline silver in the management of burns. Burns. 2004; 30: S1-S9.
12. Blair JM, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJ. Molecular mechanisms of antibiotic resistance. Nat Rev Microbiol. 2015; 13(1): 42-51.
13. Pelgrift RY, Friedman AJ. Nanotechnology as a therapeutic tool to combat microbial resistance. Adv Drug Deliv Rev. 2013; 65(13): 1803-1815.
14. Zewde B, Ambaye A, III JS, Raghavan D. A Review of Stabilized Silver Nanoparticles–Synthesis, Biological Properties, Characterization, and Potential Areas of Applications. JSM Nanotechnol Nanomed. 2016; 4(2): 1043.
15. Wei L, Lu J, Xu H, Patel A, Chen Z-S, Chen G. Silver nanoparticles: synthesis, properties, and therapeutic applications. Drug Discov Today. 2015; 20(5): 595-601.
16. Zhang X-F, Liu Z-G, Shen W, Gurunathan S. Silver nanoparticles: synthesis, characterization, properties, applications, and therapeutic approaches. Int J Mol Sci. 2016; 17(9): 1534.
17. Deepak V, Umamaheshwaran PS, Guhan K, Nanthini RA, Krithiga B, Jaithoon NMH, Gurunathan S. Synthesis of gold and silver nanoparticles using purified URAK. Colloids Surf B Biointerfaces. 2011; 86(2): 353-358.
18. Tran QH, Le A-T. Silver nanoparticles: synthesis, properties, toxicology, applications and perspectives. Adv Nat Sci Nanosci Nanotechnol. 2013; 4(3): 1-20.
19. Iravani S, Korbekandi H, Mirmohammadi SV, Zolfaghari B. Synthesis of silver nanoparticles: chemical, physical and biological methods. Res Pharm Sci. 2014; 9(6): 385-406.
20. Tien D, Liao C, Huang J, Tseng K, Lung J, Tsung T, WS Kao, TH Tsai, TW Cheng, BS Yu, HM Lin, L Stobinski. Novel technique for preparing a nano-silver water suspension by the arc-discharge method. Rev Adv Mater Sci. 2008; 18: 750-756.
21. Pluym T, Powell Q, Gurav A, Ward T, Kodas T, Wang L, Glicksman HD. Solid silver particle production by spray pyrolysis. J Aerosol Sci. 1993; 24(3): 383-392.
22. Khan M, Tarek F, Nuzat M, Momin M, Hasan M. Rapid Biological Synthesis of Silver Nanoparticles from Ocimum sanctum and Their Characterization. J Nanosci. 2017; 1-7
23. Gudikandula K, Charya Maringanti S. Synthesis of silver nanoparticles by chemical and biological methods and their antimicrobial properties. J Exp Nanosci. 2016; 11(9): 714-721.
24. Knetsch ML, Koole LH. New strategies in the development of antimicrobial coatings: the example of increasing usage of silver and silver nanoparticles. Polymers. 2011; 3(1): 340-366.
25. Tredget EE, Shankowsky HA, Groeneveld A, Burrell R. A Matched-Pair, Randomized Study Evaluating the Efficacy and Safety of Acticoat* Silver-Coated Dressing for the Treatment of Burn Wounds. J Burn Care Res. 1998; 19(6): 531-537.
26. Rustogi R, Mill J, Fraser J, Kimble R. The use of Acticoat™ in neonatal burns. Burns. 2005; 31(7): 878-882.
27. Fong J, Wood F, Fowler B. A silver coated dressing reduces the incidence of early burn wound cellulitis and associated costs of inpatient treatment: comparative patient care audits. Burns. 2005; 31(5): 562-567.
28. Chen J, Han C, Lin X, Tang Z, Su S. Effect of silver nanoparticle dressing on second degree burn wound. Zhonghua wai ke za zhi [Chinese journal of surgery]. 2006; 44(1): 50-52.
29. Cuttle L, Naidu S, Mill J, Hoskins W, Das K, Kimble RM. A retrospective cohort study of Acticoat versus Silvazine in a paediatric population. Burns. 2007; 33(6): 701-707.
30. Yang JY, Huang CY, Chuang SS, Chen CC. A clinical experience of treating exfoliative wounds using nanocrystalline silver-containing dressings (Acticoat®). Burns. 2007; 33(6): 793-797.
31. Forner Cordero I, Navarro Monsoliu R, Munoz Langa J, Alcober Fuster P, Rel Monzo P. Use of a nanocrystalline

silver dressing on lymphatic ulcers in patients with chronic lymphoedema. JWC. 2007; 16(5): 235-239.
32. Sibbald RG, Contreras Ruiz J, Coutts P, Fierheller M, Rothman A, Woo K. Bacteriology, inflammation, and healing: a study of nanocrystalline silver dressings in chronic venous leg ulcers. Adv Skin Wound Care. 2007; 20(10): 549-558.
33. Totaro P, Rambaldini M. Efficacy of antimicrobial activity of slow release silver nanoparticles dressing in post-cardiac surgery mediastinitis. ICVTS. 2009; 8(1): 153-154.
34. Miller CN, Newall N, Kapp SE, Lewin G, Karimi L, Carville K, Gliddon T, Nick M, Santamaria RN. A randomized-controlled trial comparing cadexomer iodine and nanocrystalline silver on the healing of leg ulcers. Wound Repair Regen. 2010; 18(4): 359-367.
35. Keen JS, Desai PP, Smith CS, Suk M. Efficacy of hydrosurgical debridement and nanocrystalline silver dressings for infection prevention in type II and III open injuries. IWJ. 2012; 9(1): 7-13.
36. Fries C, Ayalew Y, Penn-Barwell J, Porter K, Jeffery S, Midwinter M. Prospective randomised controlled trial of nanocrystalline silver dressing versus plain gauze as the initial post-debridement management of military wounds on wound microbiology and healing. Injury. 2014; 45(7): 1111-1116.
37. Masjedi H, Malekzad F, Marashian SM, Younespour S. The healing effect of nano-silver dressings in pemphigus vulgaris. Wounds. 2015; 2(2).
38. Sharma R, Kumar R, Mittal S, Kaur A. Study of effect of topical nano silver gel on wound healing. J Adv Med Dent Scie Res. 2016; 4(5): 59.
39. Rahaman A, Manjunath A, Bhattacharya AM. Nanosilver versus Povidone iodine dressing-efficacy in the management of chronic diabetic foot ulcers. JEMDS. 2017; 6(22): 1799-1803.
40. Wang Y, Qiao Y, Wang P, Li Q, Xia C, Ju M. Bio fabrication of silver nanoparticles as an effective wound healing agent in the wound care after anorectal surgery. J Photochem Photobiol B. 2018; 178: 457-462.
41. Verbelen J, Hoeksema H, Heyneman A, Pirayesh A, Monstrey S. Aquacel® Ag dressing versus Acticoat™ dressing in partial thickness burns: a prospective, randomized, controlled study in 100 patients. Part 1: Burn wound healing. Burns. 2014; 40(3): 416-427.
42. Trop M, Novak M, Rodl S, Hellbom B, Kroell W, Goessler W. Silver-coated dressing acticoat caused raised liver enzymes and argyria-like symptoms in burn patient. J Trauma Acute Care Surg. 2006; 60(3): 648-652.
43. Khan S, Mukherjee A, Chandrasekaran N. Silver nanoparticles tolerant bacteria from sewage environment. J Environ Sci. 2011; 23(2): 346–352.